1651

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Examining Operations

Applicant(s):	Kavalkovich, et al.	
Serial No:	09/831,424	Art Unit: 1651
Filed:	June 21, 2001	Examiner: Naff
Title:	Alginate Layer System For Chondrogenic Differentiation of Human Mesenchymal Stem Cells	
Docket No.:	640100-426	Customer No.: 27162

TRANSMITTAL LETTER

Commissioner for Patents

P.O. Box 1450

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SIR:

Enclosed please find the following:

1. Response; and
2. A self-addressed, postage paid, return receipt postcard, date stamp and return of which is respectfully requested.

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Raymond J. Lillie 8/13/03

Raymond J. Lillie, Esq. Date

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Kavalkovich, et al.
Serial No.	09/834,424
Filed:	June 21, 2001
For:	Alginate Layer System for Chondrogenic Differentation of Human Mesenchymal Stem Sells
Group:	1651
Examiner:	Naff

Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Final Rejection dated May 20, 2003, reconsideration of the above-identified application is respectfully requested.

Claims 12 – 29 stand rejected under 35 U.S.C. 103 as being unpatentable over Grande, et al. in view of Pittenger, et al.

Claims 12 – 29 stand rejected under 35 U.S.C. 103 as being unpatentable over Borland, et al. in view of Grande, et al. and Pittenger, et al.

These rejections are respectfully traversed.

In accordance with an aspect of the present invention, as defined broadly in Claim 12, there is provided a composition for producing cartilage. The composition comprises human mesenchymal stem cells in an alginate gel layer which supports the differentation and maturation of human mesenchymal stem cells into chondrocytes. The mesenchymal stem cells are contacted with a chondroinductive agent. As defined in Claim 15, the composition may further comprise hyaluronic acid.

In another aspect of the present invention, there is provided as defined broadly in Claim 18, a method for regenerating or repairing cartilage in an individual in need thereof by administering to the individual human mesenchymal stem cells in an alginate gel layer which supports the differentiation and maturation of human mesenchymal stem cells into a chondrogenic lineage to an extent sufficient to accelerate cartilage formation therefrom. The mesenchymal stem cells also are contacted with a chondroinductive agent.

In a further aspect of the present invention, there is provided, as defined broadly in Claim 23, a method of forming cartilage in vitro. The method comprises admixing human mesenchymal stem cells with a solution containing alginate. The alginate then is polymerized to form a composition comprising the human mesenchymal stem cells in an alginate gel layer. The human mesenchymal stem cells in an alginate gel layer then are coated with a chondroinductive agent.

The alginate may be sodium alginate, as defined in Claim 24. The solution may further comprise hyaluronic acid, as defined in Claim 25.

Grande discloses mesenchymal stem cells which may be contained in a polymeric matrix, such as polyglycolic acid or alginate. The mesenchymal stem cells and the carrier may be implanted into a cartilage and/or bone defect. whereby the mesenchymal stem cells will differentiate into bone or cartilage. Grande, at page 6, lines 14 – 17, states that an exogenous chondrogenic differentiating factor is not required. This is in contrast to Applicants' claimed invention in which the mesenchymal stem cells are contacted with a chondroinductive agent. Grande also does not disclose or even remotely suggest to one of ordinary skill in the art that hyaluronic acid may be added to the polymeric matrix, as defined in Claim 15.

In addition, Grande, in his working example, i.e. Example 1, describes the implantation of a polyglycolic acid matrix, including mesenchymal stem cells, into the knee joints of rabbits. As indicated at pages 21 and 22 of Grande, it was not until 12 weeks after implantation that the polyglycolic acid mesenchymal stem cell matrix showed a surface layer of cartilage which was approximately the same thickness is the host cartilage. Thus, Grande

teaches only the in vivo differentation of mesenchymal stem cells into cartilage, and does not even remotely suggest to one of ordinary skill in the art of Applicants' claimed method of forming cartilage in vitro, as defined in Claim 23.

Thus, for the above reasons and others, Grande does not render Applicants' composition and methods as claimed obvious to one of ordinary skill in the art.

Borland discloses compositions for implantation into an animal which may include an alginate polymer containing mesenchymal stem cells. The alginate gel may be used as a bulking agent in the treatment of certain reflux conditions. Borland, like Grande, does not even remotely suggest to one of ordinary skill in the art that the mesenchymal stem cells are contacted with a chondroinductive agent. Borland also does not even remotely suggest to one of ordinary skill in the art that the polymer also may include hyaluronic acid.

Although Pittenger discloses the culturing in the presence of mesenchymal stem cells in the presence of a high-glucose chondrogenic medium which also includes a transforming growth factor, in particular, TGF-β3, to induce differentiation of the mesenchymal stem cells into chondrocytes, Pittenger does not disclose or even remotely suggest to one of ordinary skill in the art a composition which comprises human mesenchymal stem cells in an alginate gel layer.

The Examiner appears to be taking the position that because Pittenger, in the second paragraph of Page 4, states that the mesenchymal stem cells are in a chemically defined serum-free environment, that the type of serum-free environment is not critical and thus it would be obvious to provide an alginate layer.

In response, in the first paragraph of Page 4, Pittenger states that "In a preferred embodiment, the hMSCs are associated in a three-dimensional format, such as a cell pellet." In addition, in the second paragraph of Page 4, Pittenger states that "the mesenchymal stem cells are preferably isolated, culture expanded human mesenchymal stem cells in a chemically defined serum-free environment and can be condensed into close proximity, such as in the form of a three-dimensional cell mass, e.g., packed cells or a centrifugal cell pellet."

As indicated in Applicants' Amendment filed February 10, 2003, Applicants have shown in Example 2 of the above identified application that under chondrogenic culturing conditions, the alginate layer provides for improved differentation of mesenchymal stem cells into chondrocytes, as opposed to the culturing of the mesenchymal stem cells in a cell pellet.

Thus, Applicants have shown that their claimed invention provides for the improved differentation of mesenchymal stem cells into chondrocytes when compared with the preferred embodiment of Pittenger. In addition, assuming solely for the sake of argument that the use of a cell pellet is not critical in Pittenger, and that the mesenchymal stem cells of Pittenger can be in any chemically defined serum-free environment, there is nothing in Pittenger that even remotely suggests to one of ordinary skill in the art that the mesenchymal stem cells may be in an alginate gel layer. Thus, Pittenger does not even remotely suggest Applicants' invention as claimed to one of ordinary skill in the art.

In addition, as stated previously, Pittenger does not even remotely suggest to one of ordinary skill in the art a composition for producing cartilage which comprises human mesenchymal stem cells in an alginate layer and hyaluronic acid, and wherein the mesenchymal cells are contacted with a chondroinductive agent, as defined in Claim 15. Although Pittenger refers to hyaluronic acid, the hyaluronic acid referred to by Pittenger is an extracellular matrix component which is produced after the mesenchymal stem cells are cultured in the chondrogenic medium, and not part of the composition for producing cartilage as defined in Claim 15. Hyaluronic acid is not present in the chondrogenic medium described in Table I on page 15. Thus, Pittenger also does not even remotely suggest to one of ordinary skill in the art the embodiment of Applicants' invention defined in Claim 15.

The combination of Pittenger, which does not even remotely suggest to one of ordinary skill in the art an alginate layer for supporting the differentation and maturation of mesenchymal cells into chondocytes, with Grande and Borland would not suggest to one of ordinary skill in the art to provide a composition comprising human mesenchymal stem cells in an alginate gel layer, wherein the mesenchymal stem cells are contacted with a chondroinductive agent, or the use of such a composition to repair or regenerate cartilage, or to form cartilage in vitro. At best the combination of Grande, Borland, and Pittenger would render it obvious to try to provide

Applicants' claimed composition and methods; however, such a standard for obviousness is improper. (See American Hospital Supply Corp. v. Travenol Laboratories, Inc., 223 U.S.P.Q. 577 (C.A.F.C. 1984), at 582, In Re Dow Chemical, 5U.S.P.Q. 2d 1529 (C.A.F.C. 1988), at 1531.) For the above reasons and others, the combination of Grande, Borland, and Pittenger does not render Applicants' claimed composition and methods obvious to one of ordinary skill in the art, and it is therefore respectfully requested that the rejections under 35 U.S.C. 103 be reconsidered and withdrawn.

Claims 16, 17, 21, 22, 28 and 29 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to convey reasonably to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

The Examiner states that support is not apparent readily in the specification for the cell density ranges required by the claims.

In response, Applicants wish to inform the Examiner that support for the cell density range of 3.2×10^6 cells/ml to 25×10^6 cells/ml is found in Example 5 at Page 16, lines 9 – 12. Support for the cell density range of 6.25×10^6 cells/ml to 25×10^6 cells/ml is found in Example 4 at Page 15, line 31 to Page 16, line 1. Therefore, support is found in the specification for the cell density ranges required by Claims 16, 17, 21, 22, 28 and 29, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

Claims 12 – 22 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to point out particularly and claim distinctly the subject matter which Applicants regard as the invention. This rejection is respectfully traversed.

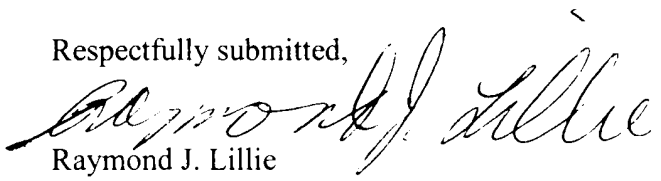
The Examiner has taken the position that the phrase "cells are contacted with a chondroinductive agent" as recited in Claims 12 and 18, is confusing in that it is unclear as to when the cells are contacted with the agent, and whether the agent is to be part of the composition.

In response, Applicants assert that such recitation is not confusing and would be understood readily by those skilled in the art. As indicated in the fourth paragraph of Page 8 of the specification, "the terms 'chondroinductive agent' or chondroinductive factor' refer to any natural or synthetic, organic or inorganic chemical or biochemical compound or combination or mixture of compounds, or any mechanical or other physical device, container, influence, or force that can be applied to human mesenchymal stem cells which are in a three dimensional format so as to effect their in vitro chondrogenic induction or the production of chondrocytes." In addition, Example 1 at Page 12 provides an example of contacting mesenchymal stem cells in an alginate layer with a medium which includes the chondroinductive agent TGF-B3.

Thus, Applicants have indicated clearly what is meant by "contacting the cells with a chondroinductive agent", and such term would be understood readily by those skilled in the art. For the above reasons and others, Claims 12 – 22 point out particularly and claim distinctly the subject matter that Applicants regard as the invention, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, second paragraph be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,



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